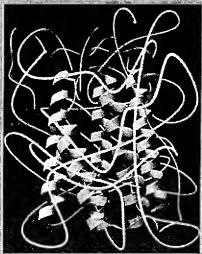


CATALOG 2005-2006

Nektar Advanced PEGylation



Polyethylene Glycol and Derivatives
for Advanced PEGylation

NEKTAR
POLYMER TECHNOLOGIES



Dear Nektar Customer,

For more than a decade, we have been working to pioneer the field of Advanced PEGylation, first as Shearwater, and now as Nektar. In that time, Nektar Advanced PEG reagents have enabled breakthrough and blockbuster products, including:

- Neulasta® (pegfilgrastim) by Amgen
- Somavert® (pegvisomant) by Pfizer
- PEGASYS® (peginterferon alfa-2a) by Roche
- PEG-INTRON® (peginterferon alfa-2b) by Schering-Plough
- Definity® (perflutren lipid microspheres) by Bristol-Myers Squibb
- Macugen® (pegaptanib) by Eyelech & Pfizer
- DuraSeal™ (PEG hydrogel) by Confluent Surgical

By working with Nektar, you, like the most successful companies in the pharmaceutical and biotechnology industry, will have access to our extensive and superior Advanced PEG reagent portfolio.

Furthermore, we understand that time is a critical factor in the development of your product. Therefore, we have 95-100% of our reagents readily available in stock at all times and able to be shipped to you within one business day.

At Nektar, we are truly dedicated to helping you develop and realize the full potential of your molecules, increasing the probability of your success and ultimately decreasing your development cost and time to market.

Contact us and let us know how we can help you create the next breakthrough product! We look forward to working with you and supporting your success with Nektar Advanced PEGylation.

Sincerely,

J. Milton Harris, Ph.D.
Chief Scientific Officer – Nektar Therapeutics, AL Division
Founder – Shearwater Corporation
2005 Nagai Innovation Award Winner

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The Value of Working with Nektar

Approvable Products with highly marketable characteristics

Nektar Advanced PEGylation is a proven technology with several FDA-approved products that have created over \$5 billion in revenues worldwide for Nektar partners.

Advanced PEG modification of therapeutics can have the following characteristics:

- Increased *in vivo* half-life (decreased enzymatic degradation and decreased kidney excretion)
- Enhanced drug performance with reduced immunogenicity, antigenicity and toxicity
- Improved physicochemical properties (improved solubility and stability)

Unique Services reaching far beyond reagents

PEG Technology

Nektar's PEG technology, comprising both research and commercial-scale manufacturing, is located in two facilities in Huntsville, Alabama and staffed by more than 160 people.

Research Facility

Our research site is a 63,000 sq. ft. facility custom-designed for research into PEG-based chemistries and the PEGylation of all molecule types. Our Advanced PEGylation Group can provide you with research services appreciated by industry-leading pharmaceutical and biotech companies.

Manufacturing Facility

Commercial-scale PEG reagent manufacturing is located in a 92,000 sq. ft. facility designed to support customers who intend to perform human clinical testing and then commercialize PEG-based drugs. Nektar has 11 production suites, and space for an additional 18 production suites, capable of manufacturing PEG reagents in batch sizes up to 25 kg.

Technical Assistance

A dedicated team of experienced technical specialists can help you solve early mission-critical issues such as guiding you toward the right type of Advanced PEG reagent(s), PEGylating your molecule in-house, providing troubleshooting advice and relevant literature references.

Development Services

The development services team at Nektar specializes in the synthesis and use of activated PEG derivatives. Depending upon your needs, these services may also include designing and manufacturing custom PEG derivatives. With broad development expertise, Nektar can help you apply and optimize PEGylation of your product or help you design engineered forms of biologics for optimal PEGylated products. If you do not see what you are looking for in this catalog, please call us and we will be happy to discuss further options of PEG reagents for your therapeutic agent or, alternatively, PEGylate your therapeutic agent for you.

Access to Advanced PEGylation

Nektar Advanced PEGylation can solve the problems associated with first-generation, low molecular weight PEGylation technologies.

First Generation PEG	Nektar Advanced PEG
Low MW activated PEGs (<12 kDa)	Low to high MW activated PEGs (1-60 kDa)
High diol content (as high as 10-15%)	Low diol content (in general less than 2%)
Non-specific PEGylation	Site-selective, site-specific PEGylation
Multiple PEGs per drug and therefore low bioactivity	Single PEG per drug and therefore high bioactivity
Physiologically unstable linkages	Physiologically stable linkages
Variable product purity	High product purity
	Custom, heterobifunctional and multi-arm PEGs
	Large scale manufacturing for marketed products



Case Studies

Research and development services moving product into clinic within 12 months

InterMune partnered with Nektar to create an improved form of consensus interferon in less than six weeks. Nektar also produced a scalable process and provided analytical characterization of the final product — all within three months — which allowed InterMune to move PEG-Alfacon (PEG consensus interferon) into Phase I clinical trials within one year.

PEGylation chemistry leading to new patent and moving drug into clinical trials

Serono partnered with Nektar to create a novel Advanced PEGylation technique to PEGylate its interferon beta molecule. After assessing the protein's structure, Nektar's development services team, working together with Serono scientists, developed a novel PEGylation strategy to first PEGylate an inaccessible cysteine within the molecule with a low molecular weight, thiol-specific PEG specially synthesized for the purpose. It was then possible to attach a high molecular weight PEG to the remaining functional group on the low molecular weight PEG. This novel, high-yield, two-step process has now been patented and Serono has initiated clinical trials with the drug.

Improved efficacy and decreased dosing frequency creating a blockbuster product

Roche partnered with Nektar to overcome certain limitations of their interferon alfa-2a (IFN) Roferon® which was associated with limited efficacy, primarily due to its short blood circulation half-life of only a few hours. The typical treatment regimen included three injections per week. Advanced PEGylation with mPEG2-NHS 40 kDa decreased clearance relative to native IFN and provided an elimination half-life of 77 hours versus nine hours. In addition, the PEGylated drug exhibited a low volume of distribution, sustained absorption from the subcutaneous injection site, and a 10-fold reduction in antibody formation. Roche's collaboration with Nektar resulted in the creation of Pegasys® (peginterferon alfa-2a), a highly successful blockbuster product for the treatment of the hepatitis C virus (HCV).

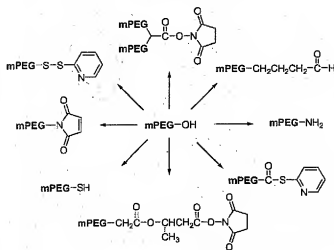


Frequently Asked Questions

What reagent should I use for PEGylation?

PEG reagents are useful for coupling to functional groups of biologically active agents such as proteins, antibody fragments, aptamers, peptides, and small molecules. The chemical attachment of PEG to these biologically active agents is referred to as "PEGylation". PEGylation reaction conditions vary depending on the biological active, the desired site and degree of PEGylation, and the PEG reagent. Factors to consider in the choice of a PEG reagent are: (1) the desired functional point of attachment (amine, thiol, carboxyl, N-terminal, etc.); (2) activity of the conjugate and its pharmacokinetics; (3) multi-PEG species (PEGmers) and positional-PEG isomers, and (4) immunogenicity of the conjugate. Nektar offers PEGylation services for our customers who wish for us to develop a PEGylation process, analytical methods, or PEG-conjugate purification.

Nektar can provide numerous activated PEGs¹



PEGylation: Reagent selection, conjugate linkage, and conjugate stability (under physiological conditions)

Carboxyl PEGylation	Conjugate Linkage Formation
mPEG-amine and a coupling agent	Amide (stable)
Amine PEGylation	
mPEG-NHS Esters	Amide
{mPEG-SMB, SPA or mPEG2-NHS}	
mPEG-Double Ester	Amide (ester linkage in the backbone is subject to hydrolysis)
{mPEG-CM.HBA.NHS}	
N-terminal PEGylation	
mPEG-ButyALD and a reducing agent	Secondary amine (stable)
mPEG-OPTE	Secondary amine (stable)
Thiol PEGylation	
mPEG-Maleimide	Sulfide (stable)
mPEG-OPSS	Disulfide [can be reduced]
mPEG-SH	Disulfide [can be reduced]

1. For simplicity, in some cases structures in this catalog are shown without defined linkers.

What is the solubility of PEG?

(1) PEGs are readily soluble in acetone, dichloromethane, chloroform, ethyl acetate, acetonitrile, N,N-dimethylformamide (DMF), and water at room temperature.

(2) PEGs are soluble in toluene, methanol, and ethanol, but may require heat to achieve dissolution.

(3) PEGs are insoluble in ethyl ether, hexanes, and isopropyl alcohol at room temperature.

What tests can be utilized to determine the number of PEGs attached following PEGylation?

Any standard protein purification/analysis technique can be employed. Techniques for consideration include sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), capillary electrophoresis, matrix assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectroscopy, and high performance liquid chromatography (HPLC). (NOTE: Peptide mapping can help determine the region of PEGylation. Liquid chromatography mass spectroscopy (LC/MS) can be used to analyze the peptide fragments.)

What are linear, branched, forked, and multi-arm PEGs?

Linear PEGs are straight-chained PEGs that are either monofunctional, homobifunctional, or heterobifunctional.

- Linear monofunctional PEGs (mPEG-X) have one reactive moiety at one end of the PEG with the other end considered non-reactive (typically end-capped with a methoxy group).
- Linear homobifunctional PEGs (X-PEG-X) contain the same reactive moiety at each end of the PEG.
- Linear heterobifunctional PEGs (X-PEG-Y) contain a different reactive moiety at each end of the PEG.

Branched PEGs (PEG2-X), also referred to as "Y-shaped" branched PEGs, contain two PEGs attached to a central core, from which extends a tethered reactive moiety.

Forked PEGs (PEG-X2) contain a PEG with one end having two or more tethered reactive moieties extending from a central core.

Multi-arm PEGs (2-arm, 3-arm, 4-arm, 8-arm PEG-X) are based upon ethoxylation of either glycerine (3-arm), pentaerythritol (4-arm), or hexaglycerine (8-arm). The 2-arm PEG was previously noted under the linear homobifunctional and heterobifunctional PEGs. Each arm has a tethered reactive group on the end. These multifunctional PEGs offer the potential to increase potency of the resulting conjugate by attaching multiple drug molecules to each arm of the PEG. Multifunctional PEGs have several applications, including linking macromolecules to surfaces (for immunoassays, biosensors, or various probe applications), hydrogel formation, and drug targeting, as well as targeting liposomes and viruses.

What is polydispersity?

All of our PEGs have some variance in the number of ethylene oxide units; this is a result of anionic polymerization. Polydispersity (PD) is a ratio that represents the broadness of a molecular weight distribution. PD is the ratio of the number average molecular weight (M_n) to the weight average molecular weight (M_w) ($PD = M_w/M_n$). If the PD is equal to 1, then M_n equals M_w and the polymer is said to be monodispersed. Typically, polymers are not truly monodispersed, although PEGs made anionically do have a low PD (1.01–1.08). As M_n changes with M_w , the PD changes (PD will always be greater than 1 for polymers).

What is the difference between Pharmacokinetics and Pharmacodynamics?

Pharmacokinetics (PK) is the movement of drugs throughout the body, including their absorption, distribution, metabolism, and excretion (A.D.M.E.), and the mathematical models that describe these actions. Pharmacodynamics (PD) is the change(s) in measurable clinical parameters related to a drug, such as increase in antitumor activity, decrease in nausea, or decrease in viral load. In other words, PD answers the question of what the drug does to the body, while PK answers the question of what the body does to the drug.

Influence of PEGylation on PK and PD of some therapeutic proteins, compared with corresponding native proteins²

Pharmacokinetic Effect	Pharmacodynamic Effect
Interferon-α2a	
Sustained absorption	In vivo antiviral increased 12- to 135-fold
Increased half-life (from 3.8h to 65h)	Antitumor activity increased 18-fold
Decreased vol. of distribution (from 31.73L to 8-12L)	Improved sustained response to chronic hepatitis C
Decreased systemic clearance (from 6.6-29.2 to 0.06-0.10 L/h)	
Interleukin-6 (IL-6)	
Increased half-life (from 2.1 to 206 min)	Thrombopoietic potency increased 500-fold
Tumor necrosis factor (TNF)	
Increased half-life 14- to 43-fold (from 3 to 45-136 min)	Antitumor-potency increased 4- to 100-fold

What is the CAS number and chemical name for PEG?

In Chemical Abstracts poly(ethylene glycol) (PEG) is described under the scientific name Poly[oxy-1,2-ethanediyl]- α -hydro- α -hydroxy with the CAS registry number of 25322-68-3. In the British Pharmacopeia the name "Macrogol" is found for PEG.

How does the PEG molecular weight (MW) affect the circulation and clearance of PEGs?

Numerous studies have demonstrated that PEGylation of biological active agents is an effective way to (1) prolong the half-life of the drug in the circulation, (2) alter the pattern of drug distribution, and (3) camouflage the drug, thereby reducing immunogenicity and protecting it from biological degradation.^{1,2}

The MW of PEG and PEG-conjugates, when injected intravenously, has a great effect on the time course of serum circulation. In general, the serum half-life of PEG extends from 18 min to 20h as the PEG MW increases

from 5 kDa to 190 kDa with a leveling-off of the serum half-life period at 20-24h for PEG and PEG-conjugates having a MW > 30 kDa or a molecular size > 8 nm.^{3,4}

Renal clearance rate of PEGs is controlled by the glomerular filtration rate in a normal kidney. The vascular wall of the renal glomeruli functions as a filter for ionic and non-ionic substances that may accumulate in the kidney through blood circulation. The excretion of these molecules can be a function of molecular size (3-5 nm) and electric charge. The glomerular filtration for the kidneys is less than 70 kDa for proteins (due to charge and molecular size) and less than 30 kDa for PEGs (due to molecular size only for nonionic, randomly coiled molecules). Short linear strands of PEG have a high clearance rate, but large linear PEGs, multi-arm PEGs, and PEGylated proteins have a slower clearance rate. This difference in renal clearance rate can be attributed to an increase in structure size, hydrodynamic volume, and a change in the total charge of the molecule.⁵

1. Mehvar R., Pharm. Pharmacol. Sci. (2000) 3, 125-136
2. Wang-Yi L., J. Biochem. Cell Biology (2002) 34, 396-402.
3. Nakaoka R. et al., J. Cont. Release (1997) 46, 253-261.
4. Brenner BM, Hostetter TH, Humes HD, Am. J. Physiol. (1978) 234, F445.
5. Ikada Y. et al., J. Pharm. Sciences (1994) 83, 601-606

Where can I learn more about PEG and PEGylation?

Additional information can be obtained from the following sources:

- Harris, J.M. and Zalipsky, S., eds, Poly(ethylene glycol), Chemistry and Biological Applications, ACS Symposium Series 680 (1997).
NOTE: This book is available from Nektar for \$160.00; Item # Q-8412-3537-6
- Veronese, F. and Harris, J.M., eds, "Peptide and protein PEGylation," *Advanced Drug Delivery Reviews* (2002) 54(4): 453-609.
- Harris, J.M. and Veronese, F.M., eds, "Peptide and Protein PEGylation II — clinical evaluation," *Advanced Drug Delivery Reviews* (2003) 55(10): 1259-1350.
- Pasut, G., Giulotto, A. and Veronese, F.M., *Expert Opin. Ther. Patents* (2004) 14(5): 1-36.
- Visit our website:
http://www.nektar.com/content/scientific_publications_ame



Note on Purity

Nektar PEG reagents are highly pure, as these reagents are intended for use in the PEGylation of pharmaceutical and related biomedical products. Nektar has devoted significant efforts to purifying and characterizing PEG derivatives. One of the synthetic challenges in derivatizing PEG is that polymeric by-products are difficult to remove because of the similar sizes and solubility of the product. Nektar PEG reagents are purified by precipitation/recrystallization and by various chromatographic methods when necessary to produce highly pure forms of PEG reagents.

Another purity concern is that methoxy-PEG (mPEG-OH) starting materials contain detectable amounts of PEG-diol as an impurity, often ranging from 0.5% up to 15% by weight. This PEG-diol impurity is problematic since the diols, upon activation, create activated bifunctional PEG side products that can be extremely difficult to remove. In addition, due to their reactivity, PEG-diol derived impurities can react with the targeted bioactive agent during coupling, thus resulting in the formation of a mixture of conjugate products. The resulting conjugate products can be difficult to purify and analyze. Nektar proprietary synthetic methods result in the formation of mPEG-reagents that are essentially free of activated bifunctional PEG side products.

At Nektar, reagent purity is determined using one or more of the following methods: nuclear magnetic resonance (NMR), gel permeation chromatography (GPC), gel filtration chromatography (GFC), matrix assisted laser desorption/ionization time-of-flight mass spectroscopy (MALDI-TOF), high performance liquid chromatography (HPLC), titration, and ion-exchange chromatography. A certificate of analysis with a summary of test results is provided with each reagent.

Unmodified PEG is typically the prime impurity found in Nektar reagents. Small molecule contaminants are virtually nonexistent, as determined by the previously mentioned methods and by gas chromatography (GC) analysis. Specific comments regarding purity of individual reagents are included in the reagent descriptions. All PEG reagents, whether custom or contained within this catalog, are made to a set of specifications using verified analytical methods. All information pertaining to test methods, specifications, results, and chemical structure are listed on the PEG-reagent certificate of analysis.

Technical note — mPEG 30 kDa quality: The linear 30 kDa mPEG reagents supplied by Nektar Therapeutics are believed to be the highest quality currently produced at large scale in the industry. With some suppliers, there have been significant problems associated with these high molecular weight reagents. These problems involved high polydispersity, high content of difunctional contaminant, and high levels of so-called truncated species (low molecular weight impurities). Responding to the need for high-quality 30K reagents, Nektar has developed methods to improve mPEG backbone quality by reducing diol content to low- to no-diol levels, thereby minimizing active truncated species in this reagent. The low- to no-diol content is key as the larger molecular weight difunctional material and the fragmentation products created during propagation/derivatization of the polymer can be controlled and removed to yield a very high-quality activated PEG in accordance with the usual Nektar standard.



Storage and Handling Conditions for PEG and PEG reagents

All PEG and PEG reagents should be stored under an inert atmosphere, in the dark, at or below -15°C.

Derivatives such as the succinimidyl active esters (e.g., mPEG-SMB and mPEG2-NHS) and maleimides react with moisture. It is therefore essential to minimize exposure to moisture and to keep these materials cold to reduce their rate of hydrolysis. PEG aldehydes (e.g. mPEG-ButyRALD) can be oxidized by atmospheric oxygen to produce the corresponding carboxylic acids, and mPEG-thiols can react with oxygen to produce disulfides. In addition, all PEGs react slowly with oxygen to form peroxides along the backbone in a process that is facilitated by light and heavy metal ions. These peroxides can lead to chain cleavage and increased polydispersity.

Shipment of PEG and PEG reagents at room temperature with no loss of activity and degradation of the backbone is possible following thorough drying and storage under an inert gas.

Before dispensing PEG and PEG reagent(s) after storage, allow the reagent to warm to room temperature. After dispensing, the reagent container should be backfilled with an inert dry gas (e.g., argon or nitrogen) and stored again at or below -15°C.

For multiple uses, consideration should be placed on dispensing the reagent upon receipt into several pre-weighed containers to reduce any risk of degradation due to cycling through multiple freeze-thaw cycles. Nektar offers custom packaging upon request at an additional charge.

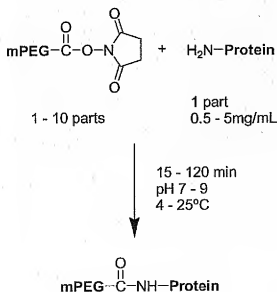


Amine PEGylation

PEG activated with electrophilic groups is useful for coupling to amino groups of biologically active molecules, such as proteins. The N-hydroxysuccinimide (NHS) ester of PEG carboxylic acids remains the most popular derivative for coupling PEG to proteins.⁸ Reaction between the epsilon amino group of lysine(s) or the N-terminal amine and the NHS ester produces a physiological stable amide linkage(s). These PEGs are extensively used for attachment of PEG to proteins, liposomes, soluble and insoluble polymers, and a variety of molecules of biological relevance. The monofunctional polymers are capped on one end by a methoxy group (mPEG) and are of particular importance due to their reactions that produce products free of cross-linking; most of our activated mPEGs have low active difunctional content (0 - 2%). Nektar offers a variety of high-quality, activated PEGs and mPEGs, including several NHS-active esters and aldehydes.

The PEG-NHS active esters can couple to the targeted therapeutic at physiological pH, but less reactive derivatives may require higher pH. Typically, PEG can be attached to a protein under normal PEGylation conditions (pH 7-9, room temperature for 30 minutes using equal molar amounts of PEG and protein). However, for some proteins it will be necessary to add up to a 10-fold molar amount of PEG relative to the protein. If the protein's amino acid composition is known, a molar ratio of PEG to protein amino groups of 1-5 to 1 will usually suffice. Increasing pH increases the rate of reaction, while lowering pH reduces the rate of reaction. Low temperature may also be employed if a labile protein is the PEGylation target. Under low temperature conditions, a longer reaction time may be warranted. Analysis of several reactions with varying ratios of PEG to protein, varying temperature, and varying pH will quickly provide information sufficient to design optimal conditions for desired degrees of PEGylation.

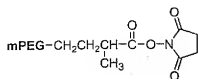
Amine PEGylation



⁸ Olson K, et al., Poly(ethylene glycol), Chemistry and Biological Applications, (1997) J.M. Harris and S. Zalipsky, eds, ACS Symposium Series 680, Washington, DC, 170-181.

Succinimidyl α -methylbutanoate

mPEG-SMB



This α -methyl substituted PEG provides a sterically hindered active ester that reacts with amino groups on biologically active agents to form a stable amide linkage. The steric effect of the α -methyl group enables greater hydrolytic stability of the active ester (2X greater than our previously successful SPA and SBA versions). The hydrolytic half-life of the mPEG-SMB is 44 minutes at pH 8, 25°C (See Table 1 for hydrolysis rate comparisons).^{9,10} This increased hydrolytic stability translates into a less reactive ester that can be more selective toward amine functional groups and more stable during protein PEGylation.

Table 1: Active Ester Hydrolysis Rates

Comparison of reactivity of various PEG derivatives as measured by hydrolysis half-lives at pH 8, 25°C, for PEG active esters measured by following UV absorbance of the succinimidyl (NHS) group. SMB and SMP hydrolysis rates were conducted at pH 8.1.

mPEG-Ester	Symbol	Half-life (min) ^a
-O-CH ₂ CH ₂ CH(CH ₃)-CO ₂ -NHS	SMB [ref 8]	44.0
-O-CH ₂ CH(CH ₃)-CO ₂ -NHS	SMP [ref 8]	33.0
-O-CH ₂ CH ₂ CH ₂ -CO ₂ -NHS	SBA [ref 7]	23.3
-O-CH ₂ CH ₂ -CO ₂ -NHS	SPA [ref 7]	16.5
mPEG2-Ester		
-O-CH ₂ CH ₂ CH(CH ₃)-CO ₂ -NHS	NHS [ref 18]	37.0

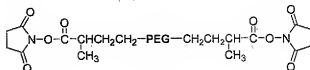
^aAminolysis rates parallel hydrolysis rates

The α -methyl enhanced hydrolytic stability can be found in other esters formed with mPEG- α -methylbutyric acid. In addition, the steric hindrance provided by the α -methyl group is expected to slow enzymatic hydrolysis in the

body. This property may be useful for delivery systems that require higher enzymatic resistance. Nektar's activated esters have been successfully applied on both proteins¹¹ and aptamers. Substitution values are 95% or greater (difunctional values are 90% or greater).

Item No.	Description	Quantity
2M4K0D01	mPEG-SMB MW 2,000 Da	500 mg 1 g 5 g
2M4K0H01	mPEG-SMB MW 5,000 Da	500 mg 1 g 5 g
2M4K0L01	mPEG-SMB MW 10 kDa	500 mg 1 g 5 g
2M4K0P01	mPEG-SMB MW 20 kDa	500 mg 1 g 5 g
2M4K0R01	mPEG-SMB MW 30 kDa	500 mg 1 g 5 g

SMB-PEG-SMB



Item No.	Description	Quantity
4K4K0F02	SMB-PEG-SMB MW 3,400 Da	500 mg 1 g 5 g
4K4K0L02	SMB-PEG-SMB MW 10 kDa	500 mg 1 g 5 g

9. SHEARWATER POLYMERS INC.; US5672662 (1999)

10. NEKTAR THERAPEUTICS; US6/37505 (2002).

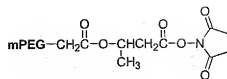
11. NEKTAR THERAPEUTICS; US Patent Application 0235734 (2004).

Roche Pharmaceuticals used Nektar PEGylation to produce PEGASYS (peginterferon alfa-2a) for the treatment of hepatitis C. Hepatitis C is an inflammation of the liver caused by the hepatitis C virus (HCV). It is the most common chronic blood-borne infection in the U.S., the leading cause of cirrhosis and liver cancer, and the number one reason for liver transplants in the U.S. According to the U.S. Centers for Disease Control and Prevention, approximately 1.8% of the U.S. population (3.9 million) has been infected with the virus. About 35,000 new cases of hepatitis C are estimated to occur in the U.S. each year. PEGylation offers several advantages to this therapeutic: (1) increased serum half-life (8-fold increase), (2) reduction in antibody formation to the drug (10-fold reduction), (3) once a week administration versus 3X per week for the native IFN, (4) increased efficacy (4X more effective in viral level reduction), and (5) ease of administration (the stability of the PEG reagent linkage allows a ready-to-use solution or liquid-filled syringe).

Item No.	Description	Quantity
223Y0L01	mPEG2-NHS	500 mg
	MW 10 kDa	1 g
		5 g
223Y0P01	mPEG2-NHS	500 mg
	MW 20 kDa	1 g
		5 g
223Y0T01	mPEG2-NHS	500 mg
	MW 40 kDa	1 g
		5 g
223Y0V01	mPEG2-NHS	500 mg
	MW 60 kDa	1 g
		5 g

Degradable Esters

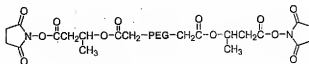
mPEG-CM-HBA-NHS



Nektar's double ester PEG reagent (mPEG-CM-HBA-NHS) contains two ester linkages. The N-hydroxysuccinimide (NHS) ester of mPEG-CM-HBA-NHS is the most active ester and readily reacts with amino groups on proteins or other amine-containing molecules under mild conditions. The second ester (between the carboxymethyl (CM) and the 3-hydroxybutanoic acid (HBA)) provides the conjugate degradability by hydrolysis in aqueous media, providing for controllable hydrolytic release of the bound molecule. The hydrolytic half-life of the second ester at pH 7, 37°C was 14 days.²¹ This derivative has been used in coupling to an enzyme²² and in forming PEG-based hydrogels.²³ Substitution values are 90% or greater (difunctional values are 85% or greater).

Item No.	Description	Quantity
OW2M0H01	mPEG-CM-HBA-NHS	500 mg
	MW 5,000 Da	1 g
		5 g

NHS-HBA-CM-PEG-CM-HBA-NHS



Item No.	Description	Quantity
OW0W0F02	NHS-HBA-CM-PEG-CM-	500 mg
	HBA-NHS	1 g
	MW 3,400 Da	5 g

21. SHEARWATER CORP.: US6515100 (2003).

22. Zhao X, Harris JM, in Poly(ethylene glycol) Chemistry and Biological Applications, J.M. Harris and S. Zalipsky, eds, ACS Symposium Series 680, Washington, DC (1997) 458-472.

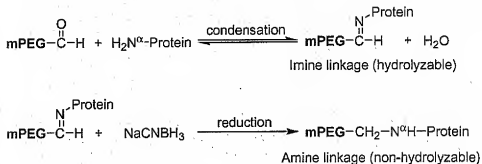
23. Zhao X, Harris JM, J. Pharm. Sci. (1996) 87: 1450-1458.



N-terminal PEGylation

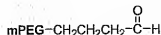
PEGs bearing aldehyde groups undergo reductive amination reactions with primary amines in the presence of a reducing reagent such as sodium cyanoborohydride. Unlike other electrophilically activated groups, PEGs bearing aldehyde groups react only with amines. This reaction takes place under mild conditions (pH 5–10, 6–36 hours) and has been shown to be useful for attaching PEG to surfaces²⁴ and proteins.^{25,26,27} The stability of the attachment (a secondary amine is formed upon reduction) is important for such applications as preparation of affinity supports and immobilized enzymes. mPEG aldehydes have also been used to form acetal linkages with hydroxyl groups of polyvinyl alcohol.²⁸ Nektar PEG aldehydes are very popular for N-terminal PEGylation of proteins and are used in one marketed product (Neulasta™) and another product in Phase II clinical trials. PEG aldehydes (such as acetaldehyde and propionaldehyde) suffer from a number of disadvantages. Acetaldehyde PEG reagents are unstable in basic media and difficult to isolate. Propionaldehyde and acetaldehyde PEG reagents have coupling challenges to proteins due to the formation of undesirable byproducts that may necessitate additional purification to obtain a pharmaceutical-grade product.

Reductive Amination (N-terminal PEGylation: α -amino group)



ButyrALDs

mPEG-ButyrALD



Nektar ButyrALD PEG reagents overcome these challenges and are also more selective and more stable at basic pH.²⁹ PEGylation of a protein or peptide with mPEG-ButyrALD conducted at pH 5–10 is believed to facilitate selective N-terminus modification due to differences in pKa values of the amino acids. The pKa for an N-terminal amine (pKa ~ 8) is lower as compared to lysine (pKa ~ 10) or Arginine (pKa ~ 12) side chain

24. Harris JA, et al., *J. Polym. Sci. Polym. Chem. Ed.* (1984) 22, 341.

25. AMGEN INC.: US5824784 (1998).

26. With P, Soupe J, Trisch D, Biehlmann JF, *Bioorg. Chem.* (1991) 19, 133-142.

27. Kinsler O, McInnes G, Treuhett M, Lodi D, Gegg C, *Adv. Drug Delivery Rev.* (2002) 54, 477-485.

28. Hanes GE, Sefton JV, *Macromol.* (1991) 24, 6065.

29. NEKTAR THERAPEUTICS AI, CORP.: WO022630 (2004).

functional groups. Selective N-terminal attachment of the polymer provides a discrete, single-positioned PEGylated isomer while in many cases preserving protein conformation and biological activity.

Amgen uses a Nektar PEG derivative in the manufacture of Neulasta™ (pegfilgrastim). The sustained duration form of Neupogen™ (Neulasta™) is used to treat neutropenia, a decrease in white blood cells resulting from chemotherapy. The benefit of PEGylation is the increased serum half-life (10-fold) resulting in a once-per-chemotherapy-cycle administration of the drug.³⁰

As with other aldehyde reagents, PEGylation between ButyrALD and an amino group of a biologically active agent involves reductive amination to provide a secondary amine linkage. Reductive amination comprises the formation of an imine linkage between the PEG and the biologically active agent, followed by reduction of the imine to provide a secondary amine linkage. The reducing step is accomplished by the addition of a reducing agent, such as sodium cyanoborohydride. Substitution values are 90% or greater (difunctional values are 85% or greater).

Item No.	Description	Quantity
082MOD01	mPEG-ButyrALD	1 g
	MW 2,000 Da	5 g
082MOH01	mPEG-ButyrALD	1 g
	MW 5,000 Da	5 g
082MOF01	mPEG-ButyrALD	1 g
	MW 20 kDa	5 g
082MOR01	mPEG-ButyrALD	1 g
	MW 30 kDa	5 g

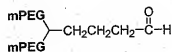
ButyrALD-PEG-ButyrALD



Item No.	Description	Quantity
0808OF02	ButyrALD-PEG-ButyrALD	1 g
	MW 3,400 Da	5 g

Branched PEG ButyrALD

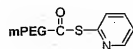
mPEG2-ButyrALD



Item No.	Description	Quantity
083YOT01	mPEG2-ButyrALD	500 mg
	MW 40 kDa	1 g
		5 g
083YOV01	mPEG2-ButyrALD	500 mg
	MW 60 kDa	1 g
		5 g

Ortho-pyridylthioester

mPEG-OPE



This o-pyridylthioester PEG reagent can provide site-specific PEGylation for the N-terminus and will not react with any other amino acid residue, unlike many other products.³¹ The requirement for this coupling is that the N-terminal amino acid be a cysteine with an unhindered thiol. Many natural products exist with a cysteine at the N-terminus, such as calcitonin³² and Big Endothelin 1.³³ In addition to these known products, the addition of a cysteine on the N-terminus of a peptide or protein can be translated in the expression, and, in many cases, should

30. Molinieux G, Current Pharm. Design, [2004] 12(11), 1235-1244.

31. SHEARWATER CORP.: WO03031581 [2003].

32. Homma T, Watanabe M, Hirase S, Kanai A, Kangawa A, Matsuo H, J. Biochemistry (1986) 100(2), 459-467.

33. Brooks C, Fugal A, J. Molecular Endocrinology (1998) 21, 307-315.

not affect the specific activity of the drug. The final result of this conjugation is an amide linkage between the mPEG and the amine group of the N-terminal amino acid. Nektar has developed several efficient methods for using this novel, site-specific coupling technology.³⁴ Substitution values are 85% or greater.

Item No.	Description	Quantity
2M3LOHD1	mPEG-OPTE	500 mg
	MW 5,000 Da	1 g
		5 g
2M3LOP01	mPEG-OPTE	500 mg
	MW 20 kDa	1 g
		5 g
2M3LOR01	mPEG-OPTE	500 mg
	MW 30 kDa	1 g
		5 g

34. NEKTAR THERAPEUTICS. Ongoing work (2005).



Thiol PEGylation

Thiol PEGylation is specific for free thiols on biological reagents. Nektar offers three PEGylation reagents for covalent modification: mPEG-MAL (forms a physiological stable linkage) and mPEG-OPSS and mPEG-SH (each forms a disulfide bond to the conjugate). Cysteine is less abundant in proteins and peptides; thus, reducing both the chance for protein deactivation and the formation of PEGmers. In addition, site specific modification (point mutation) of a cysteine is an option for site-specific PEGylation.³⁵ Cysteines engineered into a protein by site-directed mutagenesis, followed by PEGylation, have been demonstrated in animal models to enhance the regeneration of injured sciatic nerves by altering both the PK and PD properties of the protein.³⁶

Maleimides

mPEG-MAL



Coupling of maleimide to thiol groups is one of the most useful reactions for bioconjugate preparation. This reaction is highly specific for thiols at ca. pH 6.5-7.5 in the presence of other functional groups. Reaction with a thiol moiety generates a stable 3-thiosuccinimidyl ether linkage. In general, maleimides react slowly with water to form an open maleamic acid form that is slow-to-unreactive toward sulfhydryl species; hydrolysis may also occur following 3-thiosuccinimidyl formation to open up the succinimidyl ring.^{37,38} Nektar mPEG-MAL has been used as a reactive polymer for preparing well defined, bioactive PEG-protein conjugates.^{39,40} Nektar mPEG-MAL has also been used as a polymeric reagent for selective entrapment of thiol-containing peptides.⁴¹ An application of a PEG-MAL has been used in the PEGylation of staphylokinase variants that reduced by two-third the amount of antibodies elicited with wild-type staphylokinase and a 20-fold decrease in plasma clearance in acute myocardial patients.^{42,43} Three different Nektar-PEG architectures are being used in clinical trials, including one drug in Phase III. Substitution values are 85% or greater (difunctional values are 80% or greater).

35. Goodson RJ, Katre NV, Biotechnology [1990] 8, 343-346.

36. Peprinsky RB, Shapiro RI, Wong S, Chakraborty A, Gill A, Lapoge DJ, Wen D, Rayhorn P, Horan GSB, Taylor FR, Garbar EA, Galdes A, Engler TM, J. Pharmaceutical Sci. [2002] 91[2] 371-387.

37. Ishi Y, Lehrer SS, Biophys. J. [1986] 50 75-80.

38. Sym DG, Blumenfeld OO, Konigsberg W, Biochem J. [1964] 91, 589.

39. Goodson RJ, Katre NV, Biotechnology [1990] 8 343.

40. Kogan TP Synthetic Comm. [1992] 22 2417.

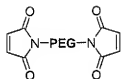
41. Romani S, et al, Chemistry of Peptides and Proteins (1984) Voelter W et al. eds., Vol. 2, 29.

42. Vanwersinckel S, Floissac S, Zhi-yong Z, Vordinfhaut I, Broepels K, Lesters I, Collen D, Jaspers I, Blood [2000] 95[3] 936-942.

43. Collen D, Simeone P, Demarein E, Moreau H, De Maeyer M, Jaspers I, Laroche Y, Van de Werf F, Circulation [2000] 102 1766.

Item No.	Description	Quantity
2F2M0H01	mPEG-MAL	1 g
	MW 5,000 Da	5 g
2F2M0P01	mPEG-MAL	1 g
	MW 20 kDa	5 g

MAL-PEG-MAL



Item No.	Description	Quantity
2F2F0F02	MAL-PEG-MAL	1 g
	MW 3,400 Da	5 g

Branched PEG Maleimide

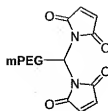
(mPEG2-MAL)



Item No.	Description	Quantity
2D3Y0T01	mPEG2-MAL	500 mg
	MW 40 kDa	1 g
		5 g
2D3Y0V01	mPEG2-MAL	500 mg
	MW 60 kDa	1 g
		5 g

Forked Maleimides

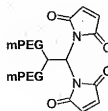
mPEG-(Forked Maleimide) (mPEG-MAL2)



Most PEGylation has been performed with linear PEG reagents. However, PEG reagents can be constructed with various architectures. Additional structures now available include the "forked" PEG reagents shown with both a linear PEG (mPEG-MAL2) and a branched PEG (mPEG2-MAL2).⁴⁴ These structures have the advantage of placing two reactive groups at a precise distance apart. These PEGs have become very popular for mimicking the heavy chain domain of an antibody and other applications where two proteins (alike or different) in proximity are advantageous. One of Nektar's partners has a forked mPEG2-MAL2 in Phase I clinical trials. Substitution values are 80% or greater.

Item No.	Description	Quantity
2D2M0H0F	mPEG-MAL2	500 mg
	MW 5,000 Da	1 g
		5 g
2D2M0P0F	mPEG-MAL2	500 mg
	MW 20 kDa	1 g
		5 g

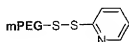
Branched PEG-(Forked Maleimide) (mPEG2-MAL2)



Item No.	Description	Quantity
2D3Y0T0F	mPEG2-MAL2	500 mg
	MW 40 kDa	1 g
		5 g

Ortho-pyridyldisulfide

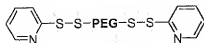
mPEG-OPSS



This thiol PEGylation reagent offers the ability to form a disulfide bond with your targeted therapeutic. There are several advantages to this reagent. First, the *o*-pyridyldisulfide (OPSS) functional group is thiol-specific for free sulfhydryls under both acidic and basic conditions (pH 3–10); readily undergoing exchange by oxidatively coupling to a free sulfhydryl group to provide a disulfide bond. The resulting disulfide linkage is stable, but reversible in a reducing environment where the linkage is converted back to the free sulfhydryl. Cleavage of the disulfide linkage is possible with reducing reagents such as DTT or mercaptoethanol. Secondly, the new disulfide formation results in the release of pyridine-2-thione, a nonreactive compound that avoids further disulfide contamination. Thirdly, the spectral property of pyridine-2-thione allows reaction monitoring by following the increased absorbance at 343 nm.⁴⁵ OPSS reagents have been successfully used in the PEGylation strategy of interferon-beta (IFN-β).⁴⁶ Substitution values are 85% or greater (difunctional values are 80% or greater).

Item No.	Description	Quantity
2M3JOH01	mPEG-OPSS	1 g
	MW 5,000 Da	5 g
2M3JOP01	mPEG-OPSS	1 g
	MW 20 kDa	5 g
2M3JOR01	mPEG-OPSS	1 g
	MW 30 kDa	5 g

OPSS-PEG-OPSS



Item No.	Description	Quantity
3J3JOFO2	OPSS-PEG-OPSS	1 g
	MW 3,400 Da	5 g

Thiols

mPEG-SH

mPEG-SH

This thiol PEGylation reagent is the free-thiol version of Nektar's activated mPEG-OPSS. As with any of our thiol PEGylation reagents, use of this PEG-thiol reagent [mPEG-SH] allows thiol-specific PEGylation of free thiols forming a disulfide-bridged polymer conjugate to the cysteine side chain of proteins and peptides. This attachment to cysteine, which is less abundant in proteins, allows for greater control of the number of attachment points and also the position of attachment. This reagent is also useful for thiol groups present in other types of active agents and small molecules. An mPEG-SH has been used in PEGylation techniques to assess tertiary and quaternary structure acquisition of biologically critical proteins. The method relies on using mPEG-MAL and mPEG-SH to quantitatively evaluate intra- and intermolecular cross-linking efficiencies.^{47,48} The Nektar proprietary synthetic method for the production of mPEG-SH minimizes disulfide formation providing free thiol-specific reagents with thiol substitution values of 90% or greater (difunctional values are 85% or greater).

Item No.	Description	Quantity
2M4FOH01	mPEG-SH	1 g
	MW 5,000 Da	5 g
2M4FOP01	mPEG-SH	1 g
	MW 20 kDa	5 g
2M4FOR01	mPEG-SH	1 g
	MW 30 kDa	5 g

SH-PEG-SH

SH-PEG-SH

Item No.	Description	Quantity
4F4FOFO2	SH-PEG-SH	1 g
	MW 3,400 Da	5 g

45. Hermanson GT, *Bioconjugate Techniques* (1996) Academic Press, Inc., 151.

46. APPLIED RES. SYSTEM: WO9955377 (1999).

47. Kovalopov A, Deutsch C, J. *Biological Chem.* (2003) 278(6) 4305-4313.

48. Robinson JM, Deutsch C, *Neuron* (2005) in press.



Heterobifunctional PEGs

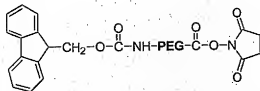
Amine-PEG-Acid (NH₂-PEG-COOH)

HCl·H₂N-PEG-COOH

Heterobifunctional derivatives of PEG have the general structure X-PEG-Y and are extremely useful as macromolecular cross-linking agents or as spacers between two different entities.^{49,50,51,52} In addition to the two independent functional groups, the presence of PEG provides water solubility, biocompatibility, flexibility, and a great degree of freedom for each of the linked components of X and Y. Applications reported in the literature include synthesis of enzymatically active cofactor-apoenzyme conjugates,⁵³ preparation of graft polymeric supports for solid-phase peptide synthesis,⁵⁴ targetable polymeric drugs,⁵⁵ and PEG-grafts onto surfaces and proteins.⁵⁶ These reagents are chromatographically purified to supply substitution values of the NH₂-PEG-COOH at 95% or greater at each end group.

Item No.	Description	Quantity
2W3T0F02	HCl·NH ₂ -PEG-COOH	500 mg
	MW 3,400 Da	1 g
		5 g
2W3T0H02	HCl·NH ₂ -PEG-COOH	500 mg
	MW 5,000 Da	1 g
		5 g

Fmoc-PEG-NHS



The 9-fluorenylmethoxycarbonyl (Fmoc) group is a standard for amine protection used in peptide synthesis for acid-sensitive reactions. This protected amine-PEG-activated acid heterobifunctional PEG offers many possibilities for tethering, cross-linking, and conjugation.⁵⁷ Typically, the NHS ester is first coupled to an amine-containing moiety. Deprotection of the Fmoc group with piperidine (e.g., 20% (v/v) for 20 minutes) provides a free amine at the other end of the PEG.^{58,59} Coupling of the PEG-amine is then performed. Substitution values are 85% or greater at each end group.

49. Sepulchre M. et al., *Makromol. Chem.* [1983] 184, 1849.

50. Zalipsky S, Barony G, J. Bioact. Compatible Polym. [1990] 5, 227.

51. Yokoyama M. et al., *Bioconjugate Chem.* [1992] 3, 275.

52. Kojima H. et al., *Eur. Polym. J.* [1988] 2, 999.

53. Nakamura A. et al., *J. Biol. Chem.* [1986] 261, 16792.

54. Zalipsky S. et al., *Peptides: Structure and Function*, [1985] V.J. Hruby and K.H. Kopple, eds. 257.

55. Zalipsky S, Barony G, J. Bioact. Compatible Polym. [1990] 5, 227.

56. Harris JM. et al., *Polymer Preprints* [1989] 30(2), 356.

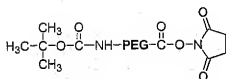
57. Leaman CP, Cooper SR, Hardee GS, *Bioconjugate Chem.*, [2003] 14(4), 738-747.

58. Bodanszky M, *Principles of Peptide Synthesis* (1993) 2nd Ed. Springer-Verlag, 298-302.

59. Fields GB, Tien Z, Barony G, *Synthetic Peptides: A User's Guide* [1992] G.A. Grant ed., W.H. Freeman and Company, New York, 81-86.

Item No.	Description	Quantity
1P4MOF02	Fmoc-PEG-NHS MW 3,400 Da	500 mg 1 g 5 g
1P4MOH02	Fmoc-PEG-NHS MW 5,000 Da	500 mg 1 g 5 g

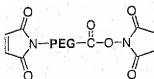
Boc-PEG-NHS



The tert-butyloxycarbonyl (Boc) protecting group is used in peptide synthesis for base-sensitive reactions. Like the Fmoc-PEG-NHS, the NHS ester is typically first coupled to an amine-containing moiety. The Boc protection group can be removed by treatment with trifluoroacetic acid (TFA) or other common acids to provide a free amine.^{60,61} Substitution values are 85% or greater at each end group.

Item No.	Description	Quantity
4M530F02	Boc-PEG-NHS MW 3,400 Da	500 mg 1 g 5 g
4M530H02	Boc-PEG-NHS MW 5,000 Da	500 mg 1 g 5 g

MAL-PEG-NHS

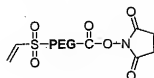


This heterobifunctional PEG contains the two most widely used functional groups for PEGylation; a thiol selective maleimide and the amine reactive NHS ester.⁶² At neutral pH, the reaction of the maleimide group with sulfhydryls is 100X faster than its reaction with amines. As the pH

increases (pH > 8.9), amines competing for maleimides is more evident. The NHS-PEG-MAL allows controllable and selective crosslinking of complementary targets by first coupling an amino group to the NHS ester, followed by coupling a sulfhydryl group to the maleimide. The versatility of this heterobifunctional PEG can be used in linking macromolecules to surfaces,⁶³ liposomes,⁶⁴ targeting of drugs, crosslinkers in peptide synthesis, and other applications. This reagent is used in a marketed product. Substitution values are 85% or greater at each end group.

Item No.	Description	Quantity
2E4MOF02	MAL-PEG-NHS MW 3,400 Da	100 mg 500 mg 1 g
2E4MOH02	MAL-PEG-NHS MW 5,000 Da	100 mg 500 mg 1 g

Vinylsulfone-PEG-NHS (VS-PEG-NHS)



Nektar offers another sulfhydryl-selective heterobifunctional PEG using the vinylsulfone functional group.⁶⁵ Sulfhydryl addition to the vinylsulfone provides a stable β -thiosulfonate linkage. While the maleimide functional group is more reactive than the vinylsulfone and sometimes works when vinylsulfone will not, vinylsulfone itself is stable in aqueous solution for days at pH 9.0, thus allowing extended reaction times for PEGylation.⁶⁶ The hydrolytic stability of the vinylsulfone group in the VS-PEG-NHS makes it an alternative candidate for amine-PEGylation followed by thiol-PEGylation. This reagent is used in a marketed product. Substitution values are 85% or greater at each end group.

60. Bodanszky M, Principles of Peptide Synthesis (1993) 2nd Ed. Springer-Verlag, 298-302.

61. Fields GB, Tien Z, Barany G, Synthetic Peptides: A User's Guide (1992) G.A. Grant ed., W.H. Freeman and Company, New York, 81-86.

62. Hermanson GT, Bioconjugate Techniques (1996) Academic Press, Inc., 228-245.

63. Andreäns JD, Chrisey LA, Nucleic Acids Res. (2000) 28(2), e5.

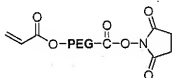
64. Leonard CF, Cooper SR, Hartley GS, Bioconjugate Chem., (2003) 14(4), 736-747.

65. VandeVondele S, Vörös J, Hubbell JA, Biotech. and Bioeng. (2003) 82(1), 784-790.

66. Morpurgo M, Veronese FM, Kochansky D, Harris JM, Bioconjugate Chem. (1996) 7, 363-368

Item No.	Description	Quantity
4M5B0F02	VS-PEG-NHS	100 mg
	MW 3,400 Da	500 mg
		1 g
4M5B0H02	VS-PEG-NHS	100 mg
	MW 5,000 Da	500 mg
		1 g

Acrylate-PEG-NHS (ACRL-PEG-NHS)

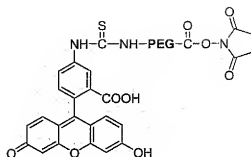


Acrylates offer the possibility of vinyl polymerization or copolymerization to produce graft polymers or cross-linked materials with excellent properties for biomaterial applications and offer a route for inclusion of peptides.^{67,68,69,70} Such materials are resistant to protein and cell adhesion and upon breakdown yield nontoxic degradation products.^{71,72} The ACRL-PEG-NHS ester offers a route for inclusion of enzymes in acrylic polymers.⁷³ The acrylate material is light sensitive and will cross-link with exposure to ultraviolet light. Substitution values are 85% or greater at each end group.

Item No.	Description	Quantity
014M0F02	ACRL-PEG-NHS	500 mg
	MW 3,400 Da	1 g
		5 g
014M0H02	ACRL-PEG-NHS	500 mg
	MW 5,000 Da	1 g
		5 g

Labeled PEGs

Fluorescein-PEG-NHS



This labeled amine PEGylation reagent has a fluorescein moiety at one end of a PEG chain and an NHS ester at the other. This heterobifunctional derivative can be coupled to proteins and other amine-containing molecules using standard amine PEGylation conditions, and provides an excellent means of monitoring attachment of the PEG. An advantage of this reagent is it possesses the same properties and most importantly the same reactivity as our most popular selling amine PEGylating reagent, mPEG-SPA. This allows PEGylation monitoring for *in-vitro* and *in-vivo* studies.⁷⁴ Substitution values are 85% or greater at each end.

Item No.	Description	Quantity
1K4M0F02	Fluorescein-PEG-NHS	500 mg
	MW 3,400 Da	1 g
		5 g
1K4M0H02	Fluorescein-PEG-NHS	500 mg
	MW 5,000 Da	1 g
		5 g

67. Gonzalez AL, Gobin AS, West JL, McIntire IV, Smith CW, *Tissue Engineering* (2004) 10: 1775-1786.

68. Herr DL, Hubbell JA, *J Biomedical Materials Res* (1998) 39: 266-276.

69. Leach JB, Bivens KA, Collins CN, Schmidt CE, *Wiley InterScience* (2004) 74:82.

70. Ium I, Elisseiff J, *Topics in Tissue Engineering* (2003) 1:25.

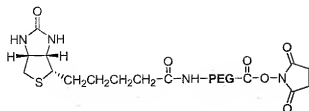
71. TORAY INDUSTRIES INC.: US4424311 (1984).

72. Sawhney AS, Pathak CP, Hubbell JA, *Macromolecules* (1993) 26: 581.

73. Yang Z, Mesiano AJ, Venkatasubramanian S, Gross SH, Harris JM, Russell AJ, *J. Am. Chem. Soc.* (1995) 117: 4843-4850.

74. Stroh M, Zipfel WR, Williams RM, Ma SC, Webb WW, Saltzman WM, *Nature Mater.* (2004) 3: 489-494.

Biotin-PEG-NHS



This biotinylation PEG reagent has several benefits. First, biotin serves as an affinity label towards biotin-binding proteins (avidin and streptavidin) due to its high binding strength and specificity for avidin.⁷⁵ Since avidin is multivalent, several biotin labels can be tethered to it.⁷⁶ Secondly, PEG is nontoxic and highly water soluble. Attachment of this reagent can result in aqueous solubility for molecules that are normally water insoluble and provide a reduction in immunogenicity. Thirdly, this reagent has an NHS ester for amine PEGylation. The resulting biotin-PEG-conjugates can then be coupled to avidin-containing molecules or surfaces, as applied in a gene delivery system for epidermal growth factor.⁷⁷ Substitution values are 85% or greater at each end.

Item No.	Description	Quantity
0H4M0F02	Biotin-PEG-NHS MW 3,400 Da	100 mg
		500 mg
		1 g
0H4M0H02	Biotin-PEG-NHS MW 5,000 Da	100 mg
		500 mg
		1 g

75. Diamandis EP, Christopoulos TK, Clin Chem. (1991) 37(5), 625-636

76. Hermanson GT, Bioconjugate Techniques (1996) Academic Press, Inc., 570-592

77. Lee H, Kim TH, Park TG, J Control Release (2002) 83(1), 109-119.



PEG Amines

mPEG-NH₂

mPEG-NH₂

Poly(ethylene glycol) chains with primary amino groups at the termini are very useful functionalized polymers.⁷⁸ The amino end group on mPEG-NH₂ is more reactive toward acylating agents than the hydroxyl group that is present on conventional PEG, and they also readily undergo reductive amination reactions. This reactivity offers a variety of methods for attachment of other molecules to the polymer via an array of stable linkages [e.g., amide, urethane, urea, secondary amine].

PEG-amine reagents can be used for:

- Preparation of conjugates of biologically active compounds^{79,80}
- Carriers for peptide synthesis⁸¹
- Preparation of PEG-coated surfaces and polymer grafts⁸²
- Preparation of PEG-glycoprotein conjugates⁸³
- Preparation of PEG-ligand conjugates for affinity partitioning⁸⁴
- Preparation of PEG-cofactor adducts for bioreactors⁸⁵

Substitution values are 90% or greater (Purity of chromatographically purified material is 98% or greater).

Item No.	Description	Quantity
2M2U0H01	mPEG-NH ₂	1 g
	MW 5,000 Da	5 g
2M2U0L01	mPEG-NH ₂	1 g
	MW 10 kDa	5 g
2M2U0P01	mPEG-NH ₂	1 g
	MW 20 kDa	5 g
2M2U0H21	mPEG-NH ₂ CP	1 g
	MW 5,000 Da	5 g
	Chromatographically Purified	

78. Backmann AE, Morr M, Johansson G. *Makromol. Chem.* [1981] 182, 1379-1384.

79. Zalapsky S, Glor C, Zilkha A. *Eur. Polym. J.* [1983] 19(12), 1177-1183.

80. Eideblom O, Yari P, Englen HC, Long HG, Greger R, Cohanichik Z. *Am. J. Physiol. Cell Physiol.* [1991] 260, C1094-C1103.

81. Pillai VNR, Mutter M. *J. Org. Chem.* [1980] 45, 5364-5370.

82. Harris JM, et al., *J. Polym. Sci. Polym. Chem. Ed.* [1984] 22, 341.

83. Urrutigoity M, Souppa J. *Biocatalysis* [1989] 2, 145.

84. Cordes A, Kula MR. *J. Chromat.* [1986] 376, 375.

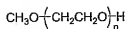
85. Okada H, Urahe I. *Meth. Enzymol.* [1987] 136, 34.



Polyethylene Glycol (PEG)

Monofunctional Linear PEGs

mPEG-OH



Nektar provides linear monofunctional PEGs that are end-capped with a methoxy group. These monomethyl ether PEGs (mPEG-OH) have a low PEG diol content, a potential crosslinking agent originating from the ethoxylation of methanol in the presence of water contamination. For mPEGs below molecular weight 10 kDa, the diol content is less than 1% and for molecular weights 10 and 20 kDa, the diol content is less than 2%. In addition, these mPEGs have a low polydispersity. Polydispersities range from approximately 1.01-1.02 for mPEG 5,000 Da to 1.02-1.03 for mPEG 20 kDa.

The activated PEG reagents manufactured by Nektar using these mPEGs is much lower as a result of purification techniques. Generating carboxylic acid intermediates of PEG permits up to 97% of diol impurities to be removed by ion-exchange chromatography before activation of the PEG reagent.⁸⁶

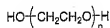
Item No.	Description	Quantity
2M000B01	mPEG-OH MW 1,000 Da	1 kg
2M000D01	mPEG-OH MW 2,000 Da	1 kg
2M000E01	mPEG-OH MW 3,000 Da	1 kg
2M000H01	mPEG-OH MW 5,000 Da	1 kg
2M000L01	mPEG-OH MW 10 kDa	1 kg
2M000M01	mPEG-OH MW 12 kDa	1 kg
2M000F01	mPEG-OH MW 20 kDa	1 kg

86. Maniandini, C. et al., *Bioconjug. Chem.* (1993) 6, 62-69.

Multi-arm PEGs

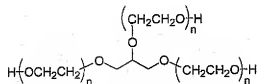
Nektar provides multi-arm PEGs prepared by ethoxylation of either glycerine (3-arm), pentaerythritol (4-arm), or hexaglycerine (8-arm). The n-value, representing the number of ethylene oxide units, may not be the same in all arms. The total molecular weight of the multi-arm PEG is a combination of the molecular weights of all the arms.

2-arm PEG (PEG diol)



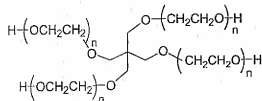
Item No.	Description	Quantity
0J000P02	PEG-diol, MW 20 kDa	1 kg

3-arm PEG



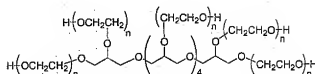
Item No.	Description	Quantity
0J000L03	3-arm PEG	500 g
	MW 10 kDa	1 kg
0J000N03	3-arm PEG	500 g
	MW 15 kDa	1 kg
0J000P03	3-arm PEG	500 g
	MW 20 kDa	1 kg

4-arm PEG



Item No.	Description	Quantity
0J000D04	4-arm PEG	1 kg
	MW 2000 Da	
0J000L04	4-arm PEG	500 g
	MW 10 kDa	1 kg
0J000N04	4-arm PEG	500 g
	MW 15 kDa	1 kg
0J000P04	4-arm PEG	500 g
	MW 20 kDa	1 kg

8-arm PEG



Item No.	Description	Quantity
0J000D08	8-arm PEG	1 kg
	MW 2000 Da	
0J000L08	8-arm PEG	500 g
	MW 10 kDa	1 kg
0J000N08	8-arm PEG	500 g
	MW 15 kDa	1 kg
0J000P08	8-arm PEG	500 g
	MW 20 kDa	1 kg
0J000T08	8-arm PEG	500 g
	MW 40 kDa	1 kg

Custom derivatives of multi-arm PEGs may also be available. Please call Customer Service at 1.800.457.1806 or +1.256.533.4201 for pricing and availability.

Ordering Information

To place an order or receive a custom synthesis quotation:

In the Americas and Europe:

Nektar Therapeutics AL, Corporation
Phone: 800.457.1806 for U.S. customers or
256.533.4201 for customers outside the U.S.
Fax: 256.533.4805
pegasales@nektar.com

New online ordering available: www.nektar.com/peg

In Asia and Australia:

Phone: 81.3.5424.6741
Fax: 81.3.5424.6769
ddsinfo@nof.co.jp
www.nektar.com/peg

You can place an order with us by fax, email or online. To expedite your order, please provide: complete "ship to" and "bill to" addresses with contact name, phone and fax number, purchase order number/payment method, item number, and quantity.

Payment Information

Payments via postal service please remit to:
Nektar Therapeutics AL, Corporation
P.O. Box 2324
Birmingham, AL 35201, U.S.A.

Payments via courier service please remit to:

Nektar Therapeutics AL, Corporation
490 Discovery Drive
Huntsville, AL 35806, U.S.A.

All payments by bank draft or check must be made in U.S. funds and have your bank routing number and account number listed, as well as the invoice number(s).

To make payments by wire transfer, add \$35 USD to the invoice amount. Our bank account information is as follows:

Compass Bank
114 Governors Drive
Huntsville, AL 35801, U.S.A.
256.532.6269
Account Number: 72096673
Routing Number: 062001186

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Please call technical support for quotes on bulk quantities. (800.457.1806 for U.S. customers or 256.533.4201 for customers outside the U.S.).

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Please call technical support for quotes on commercial manufacturing (800.457.1806 for U.S. customers or 256.533.4201 for customers outside the U.S.).

Additional Contact Information

For more information about Nektar Advanced PEGylation, or about partnering with Nektar to enable, extend, and improve your drug products, contact:

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490 Discovery Drive
Huntsville, AL 35806, U.S.A.
Phone: 800.457.1806 for U.S. customers or
256.533.4201 for customers outside the U.S.
www.nektar.com/peg

Technical and Customer Support

Nektar Therapeutics AL, Corporation
Technical Support
Phone: 800.457.1806 for U.S. customers or
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Fax: 256.533.4805
pegtechsupport@nektar.com

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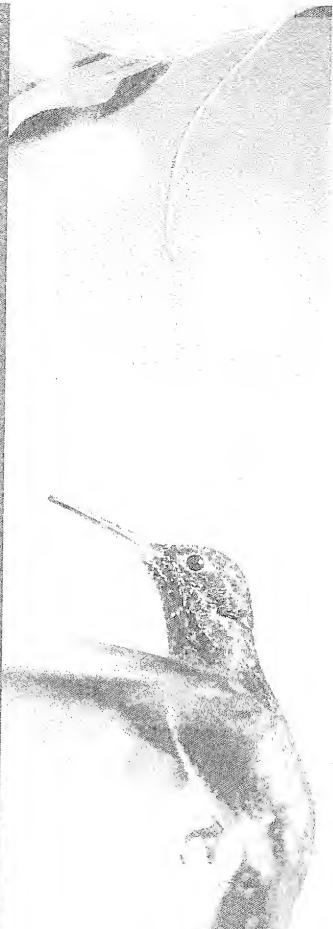
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